Clinical Management of Dying Patients

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Dying is universal, and death should be a peaceful time. Myriad comfort measures are available in the last weeks before life ends. Discussions about end-of-life issues often suffer from lack of informed opinion. Palliative care experts have identified specific somatic and psychological sources of distress for dying patients and their loved ones. Pain, shortness of breath, nausea and vomiting, and fear of abandonment contribute substantially to both physical and psychological discomfort toward the end of life. Simple, effective methods exist for relieving those symptoms. Knowledge about the natural events associated with dying and an informed approach to medical and psychological interventions contribute to systematic and successful comfort care. We describe the origin of physical and psychological distress at the end of life and provide strategies for alleviating many of the discomforts.

Death is our common destiny.[1]

Medicine encompasses more than saving lives. Assuring a patient's comfort and dignity at the time of death should be a natural part of the patient-doctor relationship. Many physicians receive inadequate training in how to manage the dying process, and many enter into such situations with limited confidence. Patient and family expectations may complicate this dilemma. Some see physicians as gatekeepers to comfort care at the end of life, but others think that they focus only on rescue from disease. They fear that medical technoogy, relentless in its obsession to cure, will extend disease into prolonged dying, perpetuate intractable pain, and strip the patient of dignity.

Such concerns are rampant, and in the past decade they have generated substantial public controversy. Debate on issues surrounding dying often stems from lack of knowledge about principles of management and available resources. The care of dying patients gets little time during medical education, and it is a scientifically neglected area that badly needs more research.* Nevertheless, contributions from palliative care specialists, hospice workers, and others have produced a substantial body of clinical knowledge and demonstrated that skilled, compassionate care can assure a comfortable and dignified death in most cases. In this article we briefly review the major sources of somatic distress in dying persons, describe the psychological needs of patients facing death, and discuss how physicians can adopt an organized and supportive approach to patient care when cure or extending life is no longer an appropriate goal.

*See N. MacDonald, MD, "Suffering and Dying in Cancer Patients—Research Frontiers in Controlling Confusion, Cachexia, and Dyspnea" on pages 278-286 of this issue.

The Dying Process

When does dying begin? For patients with slowly progressing lethal disease, it begins in a psychological sense at the time of diagnosis. For others, dying emerges suddenly in the wake of a catastrophic event. For those with a prolonged course at the end of life, death often follows a cascade of crises. Still other patients undergo enormously distressing cycles of treatment, remission, and the return of disease. The trajectory of the dying process, in part, determines patient and family needs when the end approaches. It also determines the needs that patients and families will have for information and the extent to which family members and friends can be recruited into care-providing roles.

Psychological and biologic markers signal the progression to death. Cognitive function in many terminally ill patients diminishes markedly in the weeks before death, and restlessness, air hunger, pain, and delirium are common in the last 48 hours.[2-4] Specific observable changes signal when death is imminent, usually in the days preceding the final event. Not every dying patient goes through all the changes, but knowledge that these are normal human patterns gives solace to patients, family, and friends, while guiding caretakers in providing comfort care (Table 1).[5]

Sources of Somatic Distress for Dying Patients

Articles in the medical literature indicate that unrelieved pain, shortness of breath, and nausea or vomiting are among the most common causes of somatic distress in the days, weeks, and months preceding death.[3,4,6-13] Physicians predicting the death of patients in their care should prepare to deal with these problems before they emerge.

Other noteworthy problems include confusion, restlessness, itch, disturbed bladder and bowel function, disrupted sleep, low energy, sedation, and cachexia. The last of these is often a greater source of distress to families and caretakers than to patients and is probably a natural part of preparing to die.[14] Cachexia has great practical importance because it depletes a person's energy, marks malnutrition and decline, and interferes with the ability to socialize at meal times[15]; it is particularly refractory to treatment. Rarely does any one symptom occur in isolation. The clinical challenge is to treat all discomforts without compromising the dying person's mobility or cognitive function. We discuss in detail the major somatic problems of pain, nausea and vomiting, and dyspnea.

Pain

Pain is the symptom dying patients fear the most, and although far from ubiquitous, it is a common problem in many terminal illnesses, including cancer and the acquired immunodeficiency syndrome (AIDS). Often pain is a marker of disease progression, but it can also emerge as a toxic effect of treatment or as an exacerbation of preexisting or coexisting conditions.[16] Pain interferes with activity, impedes the enjoyment of even simple satisfaction in daily living, and can prevent important and nurturing social exchanges near the end of life. It is a frequent cause of psychiatric symptoms in patients with advanced cancer. Indeed, when pain and a psychiatric disorder such as severe depression coexist, controlling the pain should be the first objective.[17]

Pain in terminally ill patients fits into two broad categories, nociceptive and neuropathic. Nociceptive pain—normal neural activity mediated by healthy intact nerves—signals tissue trauma, inflammation, or both. It can be either somatic or visceral in origin, the latter manifesting as diffuse, poorly localized distress or sometimes in patterns referred in characteristic ways to the body surface.[18] Neuropathic pain results from damage or entrapment of nerves caused by disease progression, surgical therapy,

TABLE 1.—*Signs That Death Is Near (Within a Few Days)**

Hypersomnolence
Disorientation
Irregular breathing
Excessive secretions
Visual and auditory hallucinations
Decreased clarity of sight
Decreased urine production
Mottled skin
Cool extremities
Truncal warmth

*Adapted from Hospice and Home Care of Snohomish County, Washington State.[5]

irradiation, or chemotherapy. In some patients, pain results from central lesions such as damage to the ventral or medial thalamus. Neuropathic pain has peculiar qualities that sometimes resist conventional approaches to pain control.

The most common source of nociceptive somatic pain in patients with cancer is metastasis to bone. The primary causes of pain in metastatic disease are inflammation of the periosteum and increased intraosteal pressure from tumor infiltration.[18,19] Not all of the sites that appear on a bone scan hurt; over time, a specific lesion may flare up or quiet down in unpredictable ways.[20] In some cases, bone lesions can cause fracture and acutely painful crises such as vertebral collapse. Most patients derive sufficient benefit from parenteral analgesics, but palliative irradiation of focal lesions can alleviate intransigent pain and prevent catastrophic fracture.

Visceral pain may indicate direct tumor infiltration, swelling, distension of ducts, or obstruction within organs. Inflammation can cause or exacerbate it. Because pain often elicits autonomic reflexes, visceral pain can contribute to nausea, affect bowel and bladder function, and alter appetite. When referred to the body surface, visceral pain can cause skin sensitivity in the area of referred pain and sometimes provoke muscle contracture or spasm in the affected area, thus creating more pain.[18]

Neuropathic pain syndromes include plexopathies, peripheral neuropathies, and central pain states. Pancoast's syndrome (a superior pulmonary sulcus tumor), for example, is a brachial plexopathy that causes lancinating deafferentation pain in the affected shoulder and arm.[18] Neuropathic pain differs in character from somatic pain in that it tends to occur after a delay following a causative event (for example, delayed response to pinprick), its qualities are dysesthetic (burning, "pins and needles," "electricity-like," and sometimes paroxysmal), and its somatic reference tends to follow patterns of sensory loss. Peripheral nerve injury sometimes involves exquisite tissue hypersensitivity in the absence of inflammation; patients complain that light touch and minor temperature changes cause or exacerbate pain (allodynia).

Nausea and Vomiting

Nausea and vomiting are frequent, often severe sources of distress for patients with life-threatening illness.[21] Sometimes these symptoms are iatrogenic; in other cases, they occur because of visceral lesions. They are common during cancer therapy and during the course of AIDS,[22,23] but can emerge with the use of palliative medications. Disease in a variety of organs, including the brain, may cause these symptoms. Nausea interferes with a patient's ability to move about and interact socially; it is a side effect that often limits the dosage of opioid drugs to the level of full pain relief. Vomiting, which does not always accompany nausea, is particularly dangerous because it may promote dehydration, electrolyte imbalance, aspiration pneumonia, and malnutrition. As a social event, recurrent vomiting is disastrous. Patients who need the comfort of friends refuse social contact, and family members agonize over the problem.

The mechanism and mediators of nausea and vomiting are complex and remain incompletely defined. Both central and peripheral factors play a role. The chemoreceptor trigger zone and the nucleus solitarius are located in a highly vascular area of the brain stem devoid of an effective blood-brain barrier. It is rich with opioid, dopaminergic, cholinergic, histaminergic, and serotonergic receptors. Investigators hypothesize that activation of these receptors stimulates an emetic center that, in turn, produces nausea and can initiate vomiting. A vestibular component is particularly prevalent with opioid-induced nausea and can severely limit ambulation. Impaired gastrointestinal motility, associated with diabetes mellitus, chemotherapy-induced autonomic neuropathies, opioid therapy, inactivity, and primary gastrointestinal disease, is an important cause of nausea or emesis.[24-26]

Dyspnea and Cough

Shortness of breath or dyspnea is the sense that breathing is difficult, causing a person to increase ventilation or reduce activity. It is not necessarily related to exertion.[27] Dyspnea is not synonymous with respiratory distress, which implies hypoventilation, hypoxemia, or both. Respiratory distress certainly is associated with, and a common cause of, the subjective feeling of breathlessness. Dyspnea can manifest as copious secretions, cough, chest pain, fatigue, and air hunger; its cause is complex and varied. Head and neck cancers can cause partial upper airway obstruction and often are associated with excessive secretions. Neuromuscular disease or generalized weakness will lead to restrictive airway disease with a secondary buildup of secretions that in turn can lead to obstructive lung disease. Cardiac failure can cause exertional dyspnea, tachypnea, orthopnea, paroxysmal nocturnal dyspnea, and cough. If left untreated, cardiac failure will cause pulmonary edema, which often imparts a sensation of drowning. Renal insufficiency can cause fluid overload and make cardiac failure more likely. Mediastinal disease, such as enlarged lymph nodes, can compromise both cardiac and pulmonary function, leading to dyspnea. Intra-abdominal disease—enlarging mass or ascites—will encroach on lung volumes and capacities, resulting in tachypnea to maintain minute ventilation, a common cause of subjective air hunger. Primary pulmonary disorders of many kinds can lead to dyspnea: chest wall, pleural, airway, or parenchymal tumor; infectious or aspiration pneumonitis; pulmonary embolus; bronchopleural fistula; irradiation- or chemotherapy-induced fibrosis; and chronic obstructive pulmonary disease.

Breathlessness can progress slowly over the course of a long illness, or it can present rapidly in association with acute decompensation and imminent death. It is a common feature in the last days of life.[28] Loved ones and clinicians often feel uncomfortable in the presence of a person who is short of breath.

Cough may or may not accompany dyspnea. It is often the symptom that brings a patient to medical attention and may have frightening connotations to patients and families, particularly if associated with hemoptysis. Heart failure can precipitate dry cough, but more commonly cough results from primary airway or lung disease, including pharyngeal irritation or restriction from tumor, large or small airway obstruction, reactive airway disease, mucous plugging, pleural effusion, and parenchymal disease.

Psychological Aspects of Care

Psychological factors are central considerations in the management of dying patients because the goals of care are to prevent or ease patient suffering. Careful attention to psychological aspects of the patient and family situation can help minimize family distress and bereavement. When psychological aspects of the dying process go smoothly, care providers also experience less stress.

Despite compelling reasons for emphasizing the psychological aspects of care when a patient is approaching death, some physicians ignore them. They distance themselves from the emotional needs of patients and families and continue to press on toward the unreachable goal of cure. Such behavior usually reflects insufficient training and experience in palliation. In this section, we briefly describe the psychological needs of dying patients, note the importance of family factors for the psychological aspects of care, and review several specific challenges that physicians often encounter in managing dying patients.

Needs of a Dying Patient

It is difficult to predict the psychological state and needs of a dying patient. Persons differ as a function of the trajectory of the dying process, across age cohorts, as a function of cultural background, and across levels of education and socioeconomic status. Nonetheless, certain psychological aspects of care recur frequently and merit comment.

The first is that a patient is unlikely to enter the process of dying and progress to death in a single mind set. Kübler-Ross contended that dying patients go through stages of denial, anger, bargaining, depression, and finally acceptance.[29] Her writings generated substantial controversy, but the fundamental point remains valid: the psychological needs of dying patients tend to change, and compassionate care requires that physicians tune into these changes and meet new needs as they arise.

Second, patients are vulnerable to specific fears. The most common is the fear of abandonment or dying alone in a medical technology environment separated from loved ones, that is, dying without warm human contact.[30,31] Patients often fear that they will be repulsive to others because of inadequate pain relief, poor control of bodily secretions, bad odor, and other socially offensive characteristics. It is important to protect them from the loss of self-image and feelings of isolation.

Smith and Maher found that certain attitudes can help people achieve a "healthy" death.[32] By questioning hospice coordinators, they identified the following issues of importance to people near their death:

- The presence of significant others (family, friends, or both);
- Physical expressions of caring—touching, hugging, kissing;
- A desire for the truth;
- Control in making decisions that affect care;
- Discussion of the practical issues of dying, such as finances and the family's future;
- An opportunity to review the past—pleasures, pains, accomplishments, and regrets;
- Personal appearance, cleanliness, and social presentability; and
- Religion and spirituality (independent of the patient's involvement in organized religion). Discussion of an afterlife was much less important.

Viewed collectively, these concerns suggest some important principles in the management of dying persons. Those for whom death goes smoothly are often persons who have a sense of control and involvement in decisions concerning care. They exercise opportunities to bring life to closure at a practical level, arranging their affairs and negotiating changes in family roles. They require truth and intellectual integrity rather than denial and evasion. Finally, "successful" patients are concerned about spiritual issues and the afterlife, but spiritual concerns do not equate with religiosity. This observation supports what hospice workers and chaplains have long known, that it is not necessary to be of the same religious faith as the patient to support that patient's spiritual needs.

Psychological Factors in the Family Setting

Because family members provide care, they can take important roles in the home setting—medication delivery, hygienic routines, monitoring of signs and symptoms—and they can provide organized and appropriate psychological support. Unfortunately, even healthy families may find it difficult to cope. For example, when the disease trajectory has involved many failed treatments, family members may be close to, or at, burnout. In some situations, patient and family feel that continuing survival causes everyone to suffer, and they believe collectively that death will resolve this. In such cases, it is generally best to draw on home hospice or other home care resources to take the burden off the family and to counsel them to consider the last weeks, days, or hours of a patient's life as an important time in the family history. In dysfunctional families, those with preexisting psychological problems, drug or alcohol abuse patterns, or poor family dynamics, it may require a physician advocate to protect the patient from an unnecessary conflict with a family member.[33] If certain family members tend to cause the patient stress and contribute to the suffering, it is important to direct their efforts away from the patient. Such problems are often subtle. For example, a well-meaning spouse, desperate to help and unable to accept the natural cachexia that the patient is experiencing, may insist on preparing elaborate meals, demanding that the patient eat.

In this case, it is important to identify genuine needs that the patient has and direct the spouse's energy toward meeting them.[14]

American culture leads many people to think that dying is a horrible aspect of family life, a crisis only to be endured. Counseling can help patients and families understand that the end of life is an important time, for this is when patients take stock of what they have been, make important farewells to loved ones, provide final guidance and advice for family affairs, and engage in intense meaning making. Visiting the home and talking with family members can often be a valuable investment of time in the care of dying patients.

Psychological Challenges in the Care of Dying Patients

Perhaps the most difficult problem encountered is that of distinguishing normal psychological responses to crisis, such as anxiety and sadness, from psychopathologic responses, such as depression, panic disorder, and dementia. Unrelieved pain can produce psychiatric symptoms that will disappear when pain is controlled. Sometimes long-standing patient problems (such as alcoholism) create behavioral difficulties during the dying process. A patient's personality can also present challenges. Patients who have been neurotic all their lives will be so at the end of life and may pose particular difficulties in the family environment and in interactions with caregivers. When psychological problems appear to be pivotal factors in patients' and families' suffering, a mental health professional should be consulted.

It is also challenging to form an understanding of the needs and preferences of a dying patient and to fit the delivery of care to these needs. The fundamental rule here is that good care involves giving patients options. Patients' needs are sometimes shaped in unusual ways by cultural or religious factors. Needs may change as patients pass through different stages, so options must be reviewed and assessed periodically.

Providing information that fits patients' needs near the end of life can be difficult. Patients have both the right to know and the right not to know, if they are inclined toward denial and nonconfrontation with the truth. Physicians must be ready to adjust to changes in the desire for information. The one constant is that patients always welcome the assurance that their physician values personal comfort, personal control, and patient dignity.

Finally, to some degree physicians have to care for family members as well as patients. Most family members suffer psychologically during the dying of a loved one, but eventually they will go through the process of bereavement. Bereavement is a time of physical vulnerability, and bereaved persons are more likely to suffer impaired immune status and behavioral problems.[34-36] The physician should keep in mind, therefore, that helping a patient achieve a "healthy" death benefits the survivors as well and eases their bereavement and the attendant risks to health for the survivors.

Resources and Treatment Options

No one should die in physical discomfort or in psychological distress. Pain relief—with medications, nerve blocks, epidural catheters, and palliative irradiation or surgical therapy—skilled use of antiemetics, and careful titration of sedatives, psychotropics, or stimulants can abolish or control most distressing symptoms. At times patients' comfort must take precedence over possible side effects of intervention. The doctrine of double effect invokes the axiom that intervening on a patient's behalf may incur risks, including the possibility of hastening death. To prevent discomfort, some situations require deep sedation, with the accompanying risks of respiratory or cardiovascular collapse. Practitioners should define objectives of therapy precisely, explain all possible effects of treatment, and involve patients and families in decision making to the fullest possible extent. Psychological considerations go hand in hand with medical interventions. A multidisciplinary management strategy involving patients, families, physicians, nurses, psychotherapists, pharmacists, and clergy is optimal, if available.

Giving patients a choice is fundamental to good care. Physicians and patients should plan together to determine which problems are likely to occur, decide how they want to address those problems, and where the patient wants to die, so they may arrange for home health, nursing, or hospice services, as required.

Pain Management

Analgesic medications are the mainstay of pain therapy in dying patients. Both nonopioid and opioid medications are useful. Literature on the management of cancer pain is voluminous, having culminated recently in publication of the Agency for Health Care Policy and Research's *Clinical Practice Guideline: Management of Cancer Pain.*[37] The American Pain Society's *Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain* is a pocket-sized reference with recommendations and conversion tables for the use of analgesic drugs.[38] We refer readers to those resources for a complete discussion of pain-relieving modalities. We emphasize here that clinicians should treat constant pain with fixed, around-the-clock dosing schedules, while providing liberal medication for breakthrough or incident pain as needed.

Nonopioid analgesics. Nonopioid analgesics include acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen. All nonopioid analgesics have a ceiling effect, after which higher blood concentrations produce no increase in analgesia; they are antipyretic and do not produce tolerance. Effects are additive with the central effects of opioid analgesics. Therefore, for bone pain NSAIDs can be considered the first line of defense, with opioid medications added as needed to increase pain relief. Nonopioid analgesics are useful as a component of therapy for somatic pain, have less usefulness in the treatment of visceral pain, and usually offer little or no benefit for neuropathic pain.

TABLE 2.—*Classification of Nonsteroidal Anti-inflammatory Drugs*

Classification	Drugs
Salicylic acids	Aspirin, choline-magnesium trisalicylate, salsalate, diflunisal
Acetic acids	Indomethacin, sulindac, tolmetin, ketorolac tromethamine, diclofenac sodium
Propionic acids	Ibuprofen, ketoprofen, fenoprofen calcium, flurbiprofen, naproxen
Anthranilic acids	Meclofenamate sodium
Enolic acids	
Pyrazole	Phenylbutazone
Oxicam	Piroxicam

Acetaminophen is a direct analgesic of limited potency with no notable anti-inflammatory properties. Patients can use it in combination with any other analgesic. Hepatotoxicity is the most clinically important adverse effect of acute or chronic acetaminophen overdose, although nephrotoxicity can occur also,[39] as can thrombocytopenia (very rare). Acetaminophen is an excellent antipyretic. Most patients tolerate it without difficulty.

Nonsteroidal anti-inflammatory drugs have substantial anti-inflammatory properties; they inhibit cyclooxygenase and prevent the production of prostaglandins that sensitize nociceptors in peripheral tissues. Individual response to NSAIDs varies markedly and is idiosyncratic. Table 2 shows the various classes of NSAIDs. If a particular NSAID fails to provide relief after a reasonable trial at a standard dose (usually a week) or produces uncontrollable side effects, one from another class should be tried.

The most common NSAID toxicities are gastrointestinal disturbance and bleeding. Sucralfate, histamine H_2 blockers, the antisecretory drug omeprazole, and the prostaglandin analogue misoprostol, which has both cytoprotective and antisecretory activity, provide some protection against gastric and duodenal ulceration. Misoprostol may be the only agent that is effective in patients who do not discontinue NSAID therapy.[40,41] By inhibiting cyclooxygenase, which leads to decreased thromboxane A_2 levels, most NSAIDs, including aspirin, impair platelet aggregation. Exceptions include the nonacetylated salicylates choline-magnesium trisalicylate (Trilisate)[42,43] and salsalate (Disalcid).[44]

Opioid analgesics. Misunderstandings and myths about the safety and efficacy of strong opioid analgesic medications persist. These drugs are the cornerstone of almost all analgesic strategies in the care of dying patients, present little or no risk to life, and are simple to administer. Specific confusion exists with respect to respiratory effects of opioid medications and issues of drug tolerance, addiction, dependence, and abuse (Table 3).[45]

The term "opiate" refers to any compound derived from opium. Opioids possess morphinelike qualities and bind to one or more endogenous opioid receptor sites (μ, κ, or δ receptors). "Narcotic" denotes any compound that produces sleep.[46,47] We discourage using the term "narcotic" during patient and family counseling; it carries

TABLE 3.—Opioid Tolerance, Dependence, Addiction, and Abuse

Tolerance
A predictable laboratory and clinical phenomenon in which continued use of a drug leads to decreased efficacy (intensity or duration of effect or both)

Dependence
Physical dependence implies that cessation of a drug will lead to a withdrawal syndrome; psychological dependence is an emotional need for a drug either for its positive effects or to avoid the negative effects associated with abstinence

Drug addiction
A behavioral phenomenon wherein psychological and physical dependence on a drug lead to uncontrollable use and procurement

Drug abuse
Any use of drugs that causes physical, psychological, economic, legal, or social harm to the individual abuser or others affected by the drug abuser's behavior*

*From Rinaldi et al.[45]

more drug abuse than medicinal connotation in common parlance and evokes inappropriate concerns about drug craving and loss of personal control. Patients and families frightened by the term "narcotic" often feel comfortable with "opioid."

Pure opioid agonists such as morphine, hydromorphone, methadone, and fentanyl do not have ceiling effects. Patients vary considerably in analgesic requirement and pharmacokinetics; from time to time some persons need high doses for maximum pain relief. Physicians' concerns that such doses put the patient at risk for respiratory depression or reflect drug tolerance are common but misguided.[48,49] Setting an upper limit on opioid dosing for caution's sake is inconsistent with compassionate care and can cause needless suffering. Dosing should be limited only to maximize comfort when opioid side effects such as nausea emerge as major problems. When pain becomes severe, it is often best to dose to maximize pain relief and then decrease the dose to balance the analgesia-to-side effect ratio.[50-52] Opioids should never be withheld from patients with pain from life-threatening illnesses.

Opioids are not useful for all kinds of pain. At therapeutic doses they are effective for the dull, constant aching or sharp pains associated with somatic nociceptive processes. Opioids sometimes prove ineffective when given parenterally for pain of visceral origin, especially if the pain is intermittent. When delivered into the neuraxis by either the epidural or the subarachnoid route, however, opioids control visceral pain well, stimulating receptors at the spinal level to inhibit peripheral nociceptive input.

Controversy exists about the efficacy of opioids for neuropathic pain. Many clinicians avoid the use of opioid analgesics for pain from nerve injury, preferring the use of analgesic adjuvants such as tricyclic antidepressants, anticonvulsants, benzodiazepines, corticosteroids, and neuroleptic medications under the assumption that neuropathic pain is inherently resistant to opioids.[53] More recently, investigators have shown that such pains are not resistant to opioids, but merely less responsive and may require more drug.[52] A more scientific approach to neuro-

pathic pain is to treat with an adjuvant drug, such as a tricyclic antidepressant, plus an opioid.[54]

Patients can take opioid analgesics by almost any route imaginable: oral, sublingual, parenteral, transcutaneous, rectal, neuraxial. The oral route is the first choice because it is inexpensive and dosing can be titrated easily.[55] The oral route may not be feasible in dying patients who suffer from gastrointestinal distress or dysfunction. In such cases, the parenteral route may be preferable. Most clinically useful opioids come in both oral and parenteral preparations. If intravenous access is difficult, opioids can be delivered subcutaneously by infusion or patient-controlled analgesia. A fentanyl transdermal patch (Duragesic) has been available for several years; with application every 72 hours, it can provide effective around-the-clock analgesia. Oral transmucosal fentanyl citrate has recently become available. Investigators have not yet established its use for dying patients, but early data suggest that it will be valuable in the treatment of breakthrough pain in patients who cannot swallow.[56]

We recommend that clinicians prescribe only pure opioid agonists for pain in a terminally ill patient. Of these, morphine sulfate is usually the least expensive and is available for delivery by multiple routes; oral preparations come in immediate- and sustained-release forms. Mixed agonist-antagonist or partial agonist medications, such as pentazocine, butorphanol tartrate, nalbuphine hydrochloride, and buprenorphine hydrochloride, can precipitate acute withdrawal in patients currently using morphine or another opioid, and they can block the benefits of pure opioids when additional drugs are needed for breakthrough pain.

The liver biotransforms most opioid compounds. It is important to note that even sick livers will continue that process and that the opioids have no intrinsic hepatotoxicity. The kidney and gut clear hepatic metabolites. In the presence of even mild degrees of renal failure, active metabolites may accumulate. Important examples are the metabolite morphine-6-glucuronide, which is a more potent analgesic than the parent drug, and normeperidine, a toxic by-product of N-demethylation of meperidine that can cause seizures, coma, and death. We do not recommend the use of meperidine hydrochloride for pain in chronically ill patients.

Nausea and Vomiting

Inexperienced clinicians tend to adopt a nonscientific, "shotgun" approach to administering antiemetics. Like pain, nausea responds best to around-the-clock, scheduled dosing of medications. Because several kinds of receptors stimulate the emetic center, it is sensible to employ a multidrug regimen, increasing drug doses until a positive response occurs or it causes unacceptable side effects.

Many antidopaminergic agents exist: metoclopramide hydrochloride, the butyrophenones droperidol and haloperidol, and the phenothiazines. Like NSAIDs, the effects of antidopaminergic drugs are difficult to predict and often idiosyncratic. If an agent does not work or causes undesirable side effects, switch to another within the

dopamine-blocking family. The butyrophenones and phenothiazines have a sedating effect that may be beneficial. Metoclopramide enhances gastric emptying, so it can be especially helpful in patients with decreased motility caused by disease or opioid drugs.

The histamine H_1 blockers diphenhydramine hydrochloride and hydroxyzine hydrochloride effectively inhibit the response at histamine receptors in the brain and will also counteract extrapyramidal effects that the antidopaminergic agents can cause.

The most clinically useful anticholinergic for nausea is scopolamine, available in a convenient transdermal delivery system. Single, multiple, or partial skin patches can be used, contingent on effects and side effects. A loading dose of 0.1 mg of scopolamine hydrobromide intravenously normally achieves rapid relief. Side effects are dry mouth and occasionally confusion. An alternative to scopolamine is the antihistamine dimenhydrinate; it has substantial anticholinergic activity, targeting cells in the vestibular nuclei.[57]

The serotonin-blocking agents, typified by ondansetron hydrochloride, are useful for chemotherapy-induced nausea and vomiting, especially in combination with other antiemetics,[58-60] and show some promise for the treatment of chronic nausea.

Nonspecific antiemetics include benzodiazepines, cannabinoids, the indirect-acting sympathomimetic ephedrine hydrochloride, and corticosteroids. Benzodiazepines bind to γ-aminobutyric acid receptors in the limbic system, which play no known direct role in nausea or emesis. Nevertheless, investigators have shown their use for anticipatory nausea in chemotherapy and nausea associated with anxiety, especially when used in combination with other antiemetics.[60-63] Cannabinoids also influence the limbic system and sometimes can relieve nausea refractory to other agents,[64,65] but they frequently cause cognitive and sedating side effects. Ephedrine is useful for motion sickness and nausea caused by hypotension. The mechanism by which corticosteroids work is undefined, but they also appear to be effective in combination with other antiemetics.[24,60,64,66,67]

Nonpharmacologic approaches to controlling nausea exist. Behavioral therapies for nausea and vomiting include hypnosis, cognitive behavioral training, progressive muscle relaxation, distraction, and reframing. To date, they have produced mixed results.[68-70] Behavioral methods appear useful for mild to moderate nausea but not severe problems. We recommend behavioral interventions for patients who have nausea or vomiting as an adjunct to medications, but not as a single therapy, and we note that these approaches require the patient to use a skill. When patients are approaching death, skill training is rarely appropriate. The literature suggests that acupuncture at the P6 point on the wrist may also provide relief to some patients.[71,72] This approach to nausea control merits further research.

Dyspnea and Cough

The treatment of dyspnea and cough in dying patients is similar to the general medical management of symptomatic patients without terminal disease. The objective is to treat the primary physiologic cause of the symptom to relieve the psychological distress and autonomic responses that accompany it. If the primary causes of dyspnea or cough are not treatable, then the use of sedatives and antitussives is paramount.

Bronchospastic disease may be due to infection, airway encroachment by tumor, or tobacco or other environmental causes. Bronchospasm may be reversible with the administration of β-agonists or anticholinergics by the systemic or the inhaled route, methylxanthines such as theophylline, corticosteroids, and the use of pulmonary toilet. If caused by infection, the appropriate antibiotic(s) should be used. Radiation treatment will often shrink tumors dramatically within a few days, providing considerable relief from dyspnea due to airway encroachment by mass lesions. Other cytotoxic regimens may also be appropriate, but the lag time before a beneficial effect tends to be long.

The treatment of heart failure will depend on the causes and should be tailored to the individual patient. Frequent follow-up and adjustment of medications are essential. Diuretics, inotropes, and vasodilators are the standards of therapy.

Dyspnea due to increased intra-abdominal pressure from ascites usually responds rapidly to paracentesis, although the reaccumulation of fluid is inevitable, requiring repeated drainage of fluid. Placing the patient in a comfortable sitting position is a simple and effective way to decompress intrathoracic organs.

Fluid retention from renal failure may respond to diuretics and careful fluid intake management, but refractory cases require dialysis. Clinicians should not consider the matter of renal dialysis lightly. It is invasive, cumbersome, expensive, and potentially dangerous. Patients and families should be active participants in the decision-making process. Renal dialysis may be lifesaving but may also degrade the quality of that life.

Neuromuscular disease that causes dyspnea is often troublesome to treat. Methylxanthines are the only agents available that may increase muscle strength, but the effects appear to be minimal.[73] When neuromuscular disease is severe and not reversible, mechanical ventilation is the only option. Again, the patient and the family must be active participants in the discussion, and clinicians must emphasize that mechanical ventilation almost always requires heavy sedation, which will degrade quality of life. Preliminary data in animals suggest that progestin or estradiol (or both) improve respiratory drive,[74] but these agents have no proven clinical value in humans.

Cough will often abate if it is the result of reversible upper airway, pulmonary, or cardiac disease. If due to excessive secretions from infection or chronic bronchitis, antibiotics may provide some relief. Irritation of the pharynx from chronic cough tends to perpetuate the symptom; it may be difficult to break the cycle. Anecdotal evidence suggests that a supersaturated solution of potassium iodide, three to five drops three times a day, is an effective pharyngeal lubricant. Often, sugar-coated

lozenges or candy and home remedies such as tea and honey are the best available interventions for cough due to pharyngeal irritation.

If dyspnea or cough does not respond to the above-noted interventions, then respiratory sedatives and antitussives will be necessary; opioids possess both properties. Opioids shift the carbon dioxide response curve to the right, attenuating ventilatory drive to hypercapnia. Therefore, a presumed mechanism of respiratory sedation is that patients are less aware or troubled by respiratory fatigue.[27] Alcohol, barbiturates, benzodiazepines,

and phenothiazines also act as respiratory sedatives.[75] Although not yet studied formally, haloperidol is commonly used as a respiratory sedative.[76] Our clinical experience reinforces its efficacy in that role. In addition to any direct effects on the medullary respiratory center, all of these drugs reduce anxiety and cause central sedation. In addition, the opioids decrease oxygen consumption by decreasing myocardial work, left ventricular end-diastolic pressure, and systemic diastolic pressure.

Thick or copious secretions can cause severe discomfort for both patient and loved ones. The inability to handle secretions effectively compromises the ability to

TABLE 4.—Treatment of Somatic Distress in Dying Patients

Cause of Distress	Comfort Care Modalities	Mechanism of Action	Major Side Effects	Relief of Side Effects
Pain	Acetaminophen	Analgesic, antipyretic	None except with overdose	NA
	Aspirin and NSAIDs	Analgesic, antipyretic, anti-inflammatory	GI upset and ulceration; platelet dysfunction	Antacids, sucralfate, omeprazole, H_2 blockers, misoprostol
	Opioids	Analgesic	Nausea	Antiemetics
			Constipation	Laxatives, stool softeners
			Sedation	Reduce dose, stimulants
			Pruritus	Antihistamines, nalbuphine HCl, naloxone HCl
			Urinary retention	Reduce dose, catheterize, nalbuphine HCl (?), naloxone HCl
Nausea or emesis	Scopolamine	Anticholinergic	Dry mouth, confusion	Reduce dose or discontinue
	Dimenhydrinate	Anticholinergic, antihistamine	Confusion, dry mouth	Reduce dose or discontinue
	Diphenhydramine HCl	Antihistamine	Sedation, dry mouth, confusion	Reduce dose or discontinue
	Hydroxyzine HCl	Antihistamine	Sedation, dry mouth, confusion	Reduce dose or discontinue
	Ondansetron HCl	Antiserotonin	Headache	Analgesics, discontinue
	Haloperidol, droperidol	Antidopamine	Extrapyramidal symptoms, sedation	Diphenhydramine HCl, benztropine mesylate (Cogentin), reduce dose, discontinue
	Phenothiazines	Antidopamine	Extrapyramidal symptoms, sedation	Diphenhydramine HCl, benztropine mesylate, reduce dose, discontinue
	Metoclopramide HCl	Antidopamine, gastric emptying	Extrapyramidal symptoms, sedation	Diphenhydramine HCl, benztropine mesylate, reduce dose, discontinue
	Benzodiazepines	Unknown effect on limbic system	Sedation, depression, confusion	Reduce dose, discontinue
	Cannabinoids	Unknown effect on limbic system	Sedation, confusion	Reduce dose, discontinue
	Corticosteroids	Unknown	Confusion, sleep disruption	Haloperidol may help
Dyspnea	β-Agonists	Bronchodilation	Tachycardia, restlessness	Sedative
	Anticholinergics	Bronchodilation	Tachycardia, dry mouth	
	Methylxanthines	Bronchodilation, (?) increased strength	Tachycardia, CNS signs with overdose	Decrease dose
	Opioids	Shift CO_2 response, sedation	As above	As above
	Benzodiazepines	Shift CO_2 response, anxiolysis, sedation	As above	As above
	Alcohol	Anxiolysis, sedation	Oversedation, confusion	Reduce dose, discontinue
	Barbiturates	Shift CO_2 response, anxiolysis, sedation	Oversedation, memory loss	Reduce dose, discontinue
Cough	Potassium iodide	Pharyngeal lubrication	Potassium toxicity	Discontinue drug
	Opioids	Antitussive	As above	As above

CNS = central nervous system, CO_2 = carbon dioxide, GI = gastrointestinal, HCl = hydrochloride, NA = not applicable, NSAIDs = nonsteroidal anti-inflammatory drugs

converse and often makes a horrible noise; in its extreme form, it manifests as the "death rattle." Drying agents such as scopolamine will help alleviate this problem.

Hemoptysis, or coughing up blood, is perhaps the most terrifying source of respiratory distress to patients and families. It is most common in lung cancer, affecting half or more of the patients at diagnosis[27] and about 25% of patients shortly before death.[77] Severe hemorrhage is a palliative care emergency,[78] requiring immediate intervention for the comfort of a patient and those around the patient. Death may occur within minutes. Patients, families, and practitioners should prepare for such an event. Signs of blood should be covered with bedding and towels, and a strong opioid plus a potent anxiolytic should be available to reduce the patient's awareness and fear.[27]

Conclusion

We have described the mechanisms of some of the most troublesome somatic symptoms that dying persons experience and have offered suggestions for treatment. Table 4 summarizes a sensible approach to managing those problems. At times, particularly when death is imminent, eliminating distress in an awake patient may be impossible. Comfort may require deep sedation and profound analgesia; death may come earlier as a result. This is not the same as euthanasia. The doctrine of double effect, which explains the relationship between the intended act (to provide comfort) and unintended consequence (the hastening of death), directs care providers to place the dying person's wishes first. It is essential, therefore, to clarify those wishes at the earliest possible time, to involve the dying person and loved ones in the decision process, and to state explicitly the intended results and the possible unintended consequences of treatment. We have suggested ways to assess psychological discomfort, recognizing that it is often due to somatic distress, and offer suggestions for successful intervention. Clinicians should emphasize autonomy and individuality when caring for dying patients. They should involve patients and families in all aspects of decision making when possible and nurture healthy attitudes toward the natural process of death. Heightened clinician and public awareness of available comfort care measures should promote rational debate about end-of-life issues.

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